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Feature Article

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Challenges of and Insights into Acid-Catalyzed Transformations of Sugars

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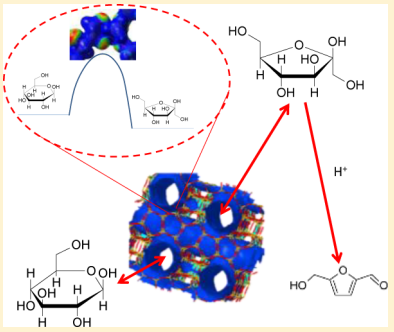
ABSTRACT: The selective transformation of hexose and pentose sugars to intermediate platform chemicals, such as furans, is an essential step in the conversion of cellulosic and hemicellulosic biomass to biofuels and biochemicals. Yet, many challenges in achieving commercially viable processes remain. In this feature article, we outline challenges that need to be overcome to enable these transformations. Then, we present the newly introduced acid-catalyzed isomerization of aldose sugars to ketose sugars via a class of solid Lewis acid catalysts (e.g., Sn-Beta, Ti-Beta). We elucidate mechanistic insights arising from subnanometer cooperativity and solvent effects that can be controlled to tune reaction pathways and selectivity and draw parallels between heterogeneous and homogeneous Lewis acid catalysts. Subsequently, we discuss fructose dehydration to 5-hydroxyl-methylfurfural (HMF) via homogeneous and heterogeneous Brønsted acid-catalyzed chemistry. We show how fundamental insights arising from the combination of kinetics, spectroscopy, and multiscale simulations rationalize the improved yield of HMF in water−organic cosolvents. The stability of heterogeneous Lewis acid catalysts under low pH enables tandem Brønsted and Lewis acid-catalyzed reactions in a single pot that overcomes equilibrium limitations and gives a high HMF yield starting from sugar raw materials. Additionally, we provide an overview of multicomponent adsorption of biomass derivatives from solution in microporous materials and discuss how structure−property relations can lead to superior micro- and micromesoporous carbon adsorbents for reactive adsorption toward high HMF yield. Finally, we provide an outlook for the field.



1. INTRODUCTION

Among renewable energy sources, biomass contains carbon and thus it is best suited for the production of fuels and chemicals. Biomass, when harvested and processed appropriately, can have a nearly "closed carbon balance", thereby leaving a minimal global-warming footprint.[1] Using biomass as a renewable energy source offers a unique opportunity for a sustainable society with unprecedented impact on the economy and energy security and independence.[1] It has been projected that, by processing ∼1.3 billion tons of biomass per year,[2] ∼33% of U.S. transportation fuel and 25% of all organic chemicals can be replaced by nonfood-interfering (lignocellulosic) biomass.[3] To meet these figures, we must go beyond cellulosic ethanol and overcome major scientific hurdles posed by the inherent complexity of biomass materials and their processing.

There are multiple processes that can convert biomass to fuels and chemicals. Most of them employ high temperatures (>400 °C) that result in unselective breaking of chemical bonds to create either a liquid fuel of poor quality or syngas (a mixture of CO and H_2), whose upgrading is very challenging. In contrast, the enzymatic or hydrolytic breakdown of lignocellulose employs low temperatures (typically <200 °C) and gives primarily monomers of biopolymers, such as cellulose- and hemicellulose-derived sugars and lignin-derived aromatic compounds. This low temperature platform is substantially more selective compared to the high temperature processes and is ideal for the production of chemicals with a number of carbon atoms similar to that of sugars.

The conversion of sugars to intermediate platforms, however, is a challenging undertaking. Major challenges include the following. (1) The sugars have very low volatility, requiring processing in solution, where solvent−solute−catalyst interactions are fairly complex. As a result, there is a general lack of fundamental understanding of these systems that, in turn, hampers the selection of solvent and catalyst and the development of fundamental models and of economically

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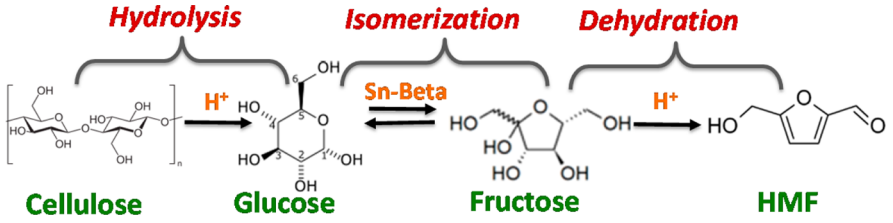
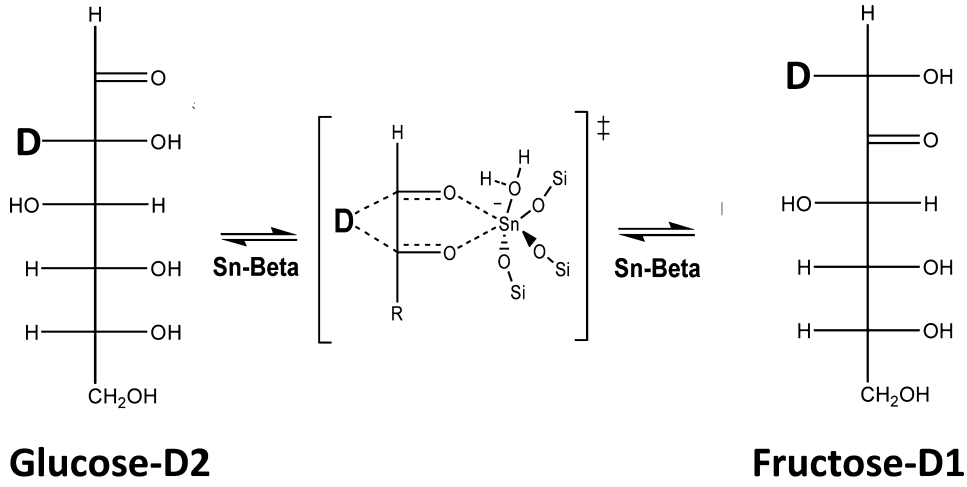
Scheme 1. Main Reaction Path from Cellulose to Glucose to Fructose to 5-Hydroxyl-Methylfurfural (HMF)



Scheme 2. Glucose to Fructose Isomerization over Sn-Beta Zeolite[a]



[a]Sugars depicted using a Fischer projection in the open conformation. D stands for deuterium in isotopically labeled sugars. Mechanism first proposed in ref 18.

viable processes. (2) The direct Brønsted-catalyzed dehydration of glucose and xylose (aldoses) to 5-hydroxyl-methylfurfural (HMF) and furfural, respectively, in water exhibits very low yields. In contrast, the dehydration of ketoses (e.g., fructose) is easier but still exhibits a low yield to desirable products, rendering processes uneconomical. Use of organic solvents instead can lead to higher yields and is feasible but separations of the products from the organic media are expensive. (3) Most prior work has focused on the Brønsted-catalyzed dehydration of fructose to HMF, whereas glucose (xylose) is the actual monomeric building block of cellulose (hemicellulose). Cellulose hydrolysis and the isomerization of glucose to fructose occurs effectively using enzymes, but these are costly, slow, and sensitive processes. The introduction of efficient thermochemical processes for these transformations (hydrolysis and isomerization) was, until recently, lacking. (4) The majority of research employs homogeneous acid catalysts whose environmental footprint can be significant. (5) Sugars contain a C═O and multiple OH functional groups, undergo tautomerization, assume multiple conformations, and their chemistry is significantly richer than that of hydrocarbons. In removing these functional groups, selectivity is key to minimize side reactions. (6) Separation schemes for biomass processing have been underdeveloped. One approach to improving yields (e.g., in the production of furans from sugars) entails use of reactive extraction, whereby the product is removed faster in an organic phase than it reacts. Currently, the fundamental thermodynamics of reactive extraction remains poorly understood and, thus, solvent selection remains an art. An alternative approach to achieve this separation entails adsorption. Understanding adsorption of biomass derivatives onto microporous materials is complicated due to the multicomponent nature of the reacting mixtures.

The Catalysis Center for Energy Innovation (CCEI), founded in the first cycle of the Energy Frontier Research Centers (EFRCs), is addressing the challenging problem of transforming lignocellulosic biomass into renewable transportation fuels and chemicals. Center members are making significant progress toward solving this grand challenge through the creation of new heterogeneous catalysts and by developing processes that leverage their capabilities. Our focus is on the hydrolytic breakdown of lignocellulose into its building blocks and the subsequent upgrade of the sugars into intermediate versatile platforms, such as furfural and HMF, which can be converted to fuels and chemicals. The importance of these two chemicals has motivated a vast number of fundamental and applied studies; the results of which are summarized in several recently published reviews.[4−7] The overall paths for the production of C6 sugars and HMF are shown in Scheme 1. Similar paths exist also for the C5 sugars. In this feature article, we provide an overview of the progress made in CCEI on the selective transformation of sugars to intermediate platform chemicals and the physicochemical lessons resulting from our work. We close with a summary and outlook.

2. SUGAR CHEMISTRY VIA LEWIS ACID CATALYSTS

2.1. Sugar Chemistry in Lewis Acid Beta Zeolites. *2.1.1. Glucose to Fructose Isomerization in Sn-Beta.* A challenge in converting biomass through its monomeric substituents, specifically the glucose and xylose monosaccharides that comprise cellulose and hemicellulose, is to design and develop catalysts that can selectively control the reactivity of

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these highly functionalized and highly oxygenated sugar monomers. For example, glucose in its ring-open form contains a carbonyl (C═O) functionality in the form of an aldehyde group located at the C1 position and five hydroxyl (−OH) groups residing at the C2−C6 positions along the carbon backbone (Scheme 2). Reactions involving the aldehyde end of glucose have a rich history in the field of organic chemistry and include: (i) ring-closing and ring-opening via reversible hemiacetal formation, (ii) aldose-ketose isomerization via base-catalyzed abstraction of the α-carbonyl proton and reversible enolate formation (Lobry de Bruyn-Alberda van Ekenstein rearrangements reported in 1895),[8,9] and (iii) retro-aldol fragmentation and recombination initiated by base-catalyzed α-carbonyl proton abstraction (reported by Fischer in 1890).[10] Such reactions of sugars can be catalyzed by homogeneous alkali hydroxides or heterogeneous solid bases, but enolate intermediates generated by base catalysts lead to the formation of many side products and to sugar degradation reactions with increasing conversion.[11−13]

One approach to the creation of useful compounds from biomass within the CCEI has been to explore alternate catalytic strategies for selectively reacting carbonyl functions in sugars, namely through the synthesis and catalysis of a class of materials that contain Lewis acid centers (Sn^{4+}, Ti^{4+}) isolated within the frameworks of hydrophobic, silica-based molecular sieves. In contrast to bases that selectively react with acidic α-carbonyl protons in sugars, Lewis acid centers selectively coordinate with the carbonyl oxygen atom and can also chelate with other oxygen atoms in nearby alcohol groups (Scheme 2).[14] Lewis acidic Sn sites in molecular sieves with the zeolite beta topology (Sn-Beta) have been shown to catalyze intermolecular Meerwein-Ponndorf-Verley carbonyl reduction and Oppenauer alcohol oxidation (MPVO) cycles, via concerted binding of an aldehyde or a ketone molecule and a separate alcohol molecule.[15−17] Analogously, Sn sites in zeolite beta have also been shown to selectively catalyze glucose−fructose isomerization in water,[18] via the concerted binding of the C1 aldehyde oxygen and the C2 hydroxyl oxygen in ring-opened glucose chains prior to an intramolecular MPVO reaction cycle.[19] This Lewis acid-catalyzed isomerization reaction mechanism on Sn-Beta, where Lewis acidic Sn centers catalyze the ring-opening of glucose chains and the intramolecular H-shift from the C2 to C1 position on open glucose chains, is analogous to the reaction mechanism mediated by D-xylose isomerase metalloenzymes.[20] The active sites of these metalloenzymes are comprised of two Lewis acidic metal centers (e.g., Mg^{2+}, Mn^{2+}) that are confined within a hydrophobic pocket.[21,22] These features (Lewis acidity and hydrophobicity at the active site) are also characteristic of synthetic molecular sieves that are shown to catalyze stereoselective sugar rearrangements (Figure 1).[18,20,23−25]

A critical feature of the active site in Sn (or Ti)-Beta for the selective glucose−fructose isomerization is the presence of an isolated Lewis acid center in a tetrahedral position of the silica-based molecular sieve framework (Figure 1). In the case of Sn-Beta, the ^{119}Sn magic angle spinning nuclear magnetic resonance (MAS NMR) spectroscopy can be used to unambiguously distinguish framework Sn sites from extraframework Sn species located in SnO_2 particles (not part of the silica framework). Framework Sn sites bind two water molecules and give resonances for octahedral Sn (−685 to −700 ppm) in hydrated forms of Sn-Beta that shift upon dehydration of the sample to give resonances for tetrahedral Sn (−420 to −445 ppm).[20] In contrast, extraframework SnO_2 species give resonances for octahedral Sn centered at −604 ppm in both hydrated and dehydrated forms of the sample.[23] Mechanistic studies using isotopically labeled (^{2}H, ^{13}C) glucose reactants show that, although both framework Sn sites and extraframework SnO_2 clusters are able to catalyze glucose−fructose isomerization in liquid water, only the former sites do so via the Lewis acid intramolecular C2−C1 hydride shift mechanism;[19] the extraframework SnO_2 functions via the base-mediated proton transfer mechanism.[23] Framework Sn centers in their "open" configuration (three −OSi bonds and one −OH group; Figure 1) can also be distinguished from those in their "closed" configuration (four −OSi bonds) by solid-state ^{119}Sn NMR spectroscopy, because only resonances of the "open" Sn sites in dehydrated samples (−420 ppm) cross-polarize with ^{1}H nuclei.[20] Theoretical calculations also suggest that these "open" framework Sn sites isomerize glucose to fructose with a lower barrier than "closed" framework Sn sites because the stannanol (Sn−OH) group mediates proton-transfer steps with hydroxyl groups on bound, open-chain sugars before and after the kinetically relevant intramolecular C2−C1 H-shift step.[20]

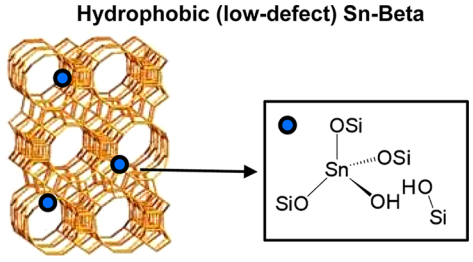

Figure 1. Active sites in synthetic materials that have been shown to catalyze stereoselective sugar reactions in liquid media are comprised of (i) a Lewis acid center (Sn is shown) in the "open" configuration that is isolated and (ii) within a hydrophobic (low-defect) molecular sieve.

Formally, the H-shift from C2 to C1 is referred to as a hydride (H^-) transfer,[19,26−31] which theoretically may follow one of four possible pathways, each leading to the same result albeit with different energy requirements: (i) the one-step, strict hydride-ion transfer, with two electrons, all along the reaction coordinate; (ii) an H atom transfer followed by electron transfer ($H + e^-$); (iii) electron transfer followed by an H atom transfer [$e^- + H$, the reverse of (ii)]; and (iv) sequential electron−proton−electron transfer ($e^- + H^+ + e^-$). A migrating hydrogen may be described as "hydridic" in character if it bears a negative partial charge.[32−35] Theoretical calculations (natural bond orbital analysis) for aldose−ketose isomerization in Sn-Beta show, however, positive charge on the transferring H in the transition state, giving no hint of hydridic character, even though there is clear charge transfer from one side of the C2−C1 bond to the other attendant upon the H shift.[36] The theoretical data do not support the modes (iii) and (iv) either but are more in consonance with a concerted $H + e^-$ mechanism [mode (ii)]. In this mode, the H and the electron transfers involve different centers, namely, the H-donor is not the same atom as the e^--donor and the H-acceptor is not the same as the e^--acceptor. As the H atom transfers from C2 to C1, the coupled electron transfer occurs adiabatically from O2 to O1. This picture is consistent with NBO analysis, according to which, in the chelate-forming transition state, the C2−O2 and C1−O1 double bonds are, respectively, partially formed and partially broken. The transferring electron comes from the

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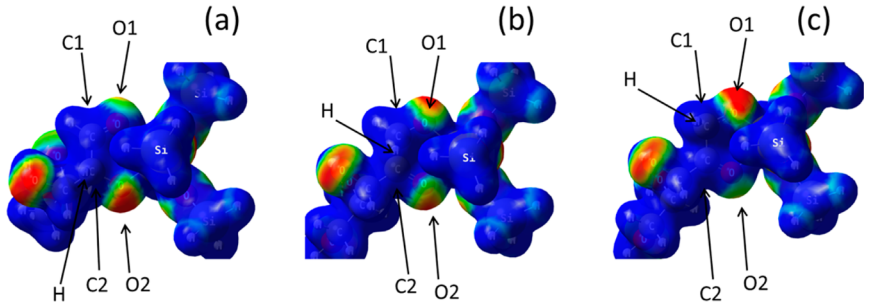

Figure 2. Evolution of the electron density during the hydrogen migration from the C2 to the C1 carbon. High electron density regions are shown in red and low density regions in blue. The electron density surface corresponds to the 0.02 e/Å^3 level. (a) Intermediate with the H atom on C2; (b) chelate-forming transition state with the H atom midway between C1 and C2; (c) intermediate following with the H atom on C1. Reprinted from ref 36. Copyright (2013), with permission from Elsevier.

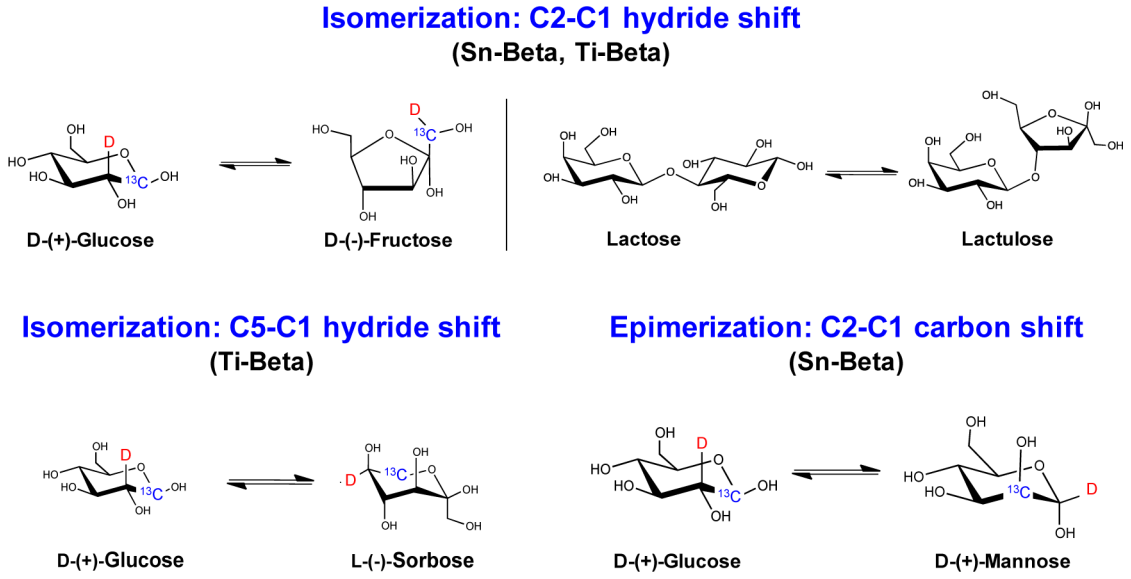

Figure 3. Stereoselective sugar rearrangements that have been shown to be catalyzed by hydrophobic Lewis acid zeolites (Sn-Beta, Ti-Beta) in liquid water and methanol (353−413 K). Details about experimental conditions can be found in refs 18−20 and 25 (top), ref 24 (bottom, left), and refs 23 and 48 (bottom, right).

O2 lone pair in the p-orbital that is normal to the chelate ring and is donated to the O1 p-orbital that participates in the double bond with C1. Owing to the short transfer range between the O1 and O2 oxygen atoms, the coupling between the donor and acceptor orbitals on the oxygen atoms is strong. This is evident from the delocalized nature of the highest occupied molecular orbital of the transition state. The situation is similar to that of PCET (proton-coupled electron transfer) reactions that involve four rather than two atoms, owing to the proton and electron donor/acceptor atoms not being the same.[37−39] In Figure 2, we show a mapping of the electrostatic potential onto the electron density and how it evolves from the state prior to the H-shift to the chelate-forming transition state and on to the intermediate following the H-shift. The electron density at the transferring H atom and at the C1 and C2 carbon atoms does not change as the hydrogen is migrating, which indicates that the hydrogen atom is not carrying any extra charge with it. Only the electron densities at the O1 and O2 oxygen atoms vary and, in the transition state, the transferring electron appears to be shared between the two of them.

2.1.2. Effect of Hydrophobicity. Another critical feature of the active site in Sn(Ti)-Beta for glucose−fructose isomerization catalysis in liquid water is the presence of hydrophobic channel environments surrounding active Sn or Ti centers in the molecular sieve framework (Figure 1). Sn- and Ti-Beta can be synthesized with very low defect (silanol group) density when crystallized in fluoride media at near neutral pH or with much higher defect site density when crystallized in hydroxide media at higher pH.[40] Molecular sieves with low defect density are hydrophobic, evident in very low micropore water uptakes (ca. 1% of total micropore volume) detected in single-component water vapor adsorption isotherms (293 K).[41] The hydrophobic nature of defect-free channels of beta zeolite are also reflected in negligible water uptakes on samples following the adsorption of glucose from aqueous solutions, assessed experimentally by thermogravimetric analysis/differential scanning calorimetry and by ^{13}C and ^{1}H solid-state NMR,[41] and assessed theoretically by Gibbs ensemble Monte Carlo simulations.[42] Kinetic studies show that glucose−fructose isomerization rate constants measured in liquid water are factors of ∼10−30 higher (373 K) for Ti centers located in hydrophobic rather than hydrophilic, silica-based solids, because hydrophobic surroundings help mitigate the competitive adsorption and inhibition of water molecules onto Lewis acid centers.[25] These effects are similar to the mechanistic role of hydrophobic pockets in D-xylose isomerase

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metalloenzymes to exclude bulk water from active site pockets during isomerization catalysis.[21]

2.1.3. Catalyst Stability. Practical implementation of the Sn(Ti)-Beta zeolites in sugar isomerization and integrated or one-pot reaction schemes requires assessment of their stability under reaction conditions (e.g., zeolite dissolution, Sn leaching) and determination of reaction (desirable reactions vs byproduct formation) and deactivation kinetics. Byproduct formation by retro-aldol, aldol condensation, dehydration, rehydration, and hydride shift reactions has been documented but not completely quantified yet. However, as revealed by a phenomenological model developed recently,[43] byproduct formation is significant even at low conversions and along with catalyst deactivation constitute subjects for further work before considering commercialization of this technology.

2.1.4. Other Transformations of Glucose. Hydrophobic molecular sieves containing isolated, framework Lewis acid centers have been shown to mediate glucose−fructose isomerization and a much wider range of related, stereoselective sugar rearrangements (Figure 3). Sn-Beta catalyzes isomerization reactions of smaller sugars than glucose (C_5,[44,45] C_4,[46] and C_3[45,47]) and even of larger disaccharides, such as lactose (a glucose-galactose dimer) to lactulose (a fructose-galactose dimer), which involves the isomerization of a glucose subunit within the disaccharaide to a fructose subunit (Figure 3).[25] Sn-Beta can also catalyze the glucose−mannose epimerization by an intramolecular carbon shift of the C1 center to the C2 position known as the Bilik reaction mechanism (Figure 3), and this reaction is promoted both in methanol solvent[23] and in the presence of borate salts in water.[48] Recently, Ti-Beta has been shown to uniquely catalyze a stereoselective isomerization of D-glucose to L-sorbose via a direct, intramolecular C5−C1 hydride shift (Figure 3), for which there are no metalloenzyme or catalytic analogs.[24]

Theoretical calculations for glucose isomerization or epimerization to fructose or mannose, respectively, have suggested that cooperativity between the Lewis acid center and the neighboring silanol group at the open active site of Sn-Beta may be playing a significant role in the catalysis.[49] With dependence on whether the silanol group vicinal to the stannanol is an active participant or a mere spectator, the isomerization reaction may follow two distinct pathways that correspond to two different binding modes of the sugar molecule to the active site. Glucose can bind with similar energies either via a hydrogen bond between the C1═O group and the vicinal Si−OH (monodentate mode) or via the lone pair of the C1═O oxygen and Sn and a hydrogen bond between the C2−OH and the stannanol (bidentate mode). Formally, the reaction proceeds via proton transfer from C2−OH to Sn−OH, hydride transfer from C2 to C1 and proton back-donation to C1═O. Common to both pathways is the initial proton transfer and the formation of a ligand water molecule on the Sn center. The proton transfer is somewhat more facile in the monodentate mode, by ca. 5 kcal/mol. Mechanistically, the two pathways bifurcate at the next step: in the monodentate mode, the C2−C1 hydride transfer, and the final proton back-donation take place in a concerted fashion with the direct participation of the ligand water and of the vicinal silanol, as shown in Figure 4; in the bidentate mode, a stepwise mechanism is followed, whereby the hydride transfer proceeds through a chelate-forming transition state, with the proton back-donation trailing it. The concerted mechanism is energetically more favorable by ca. 5 kcal/mol. Interestingly,

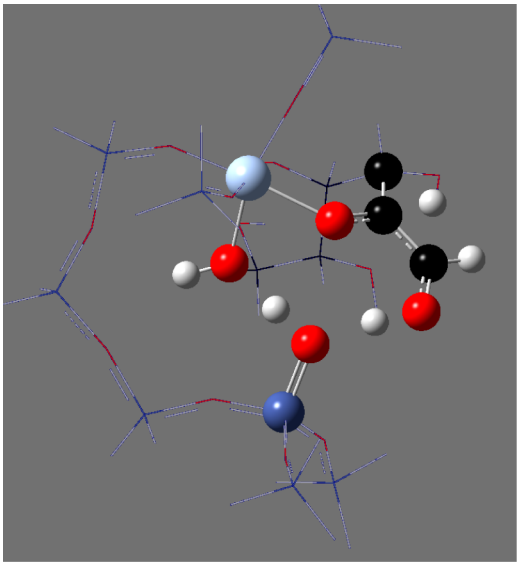

Figure 4. Concerted hydride and proton transfers in the isomerization of glucose to fructose in Sn-Beta, with participation of the silanol group vicinal to the stannanol group. From quantum chemical calculations with the active site being modeled with a cluster of 49 atoms (8 Si, 1 Sn, 10 O, and 20 H atoms) and the M06-2X density functional. (Black balls, C; blue, Si; red, O; cyan, Sn; and white, H). Reprinted with permission from ref 49. Copyright 2013 American Chemical Society.

the energetic requirements for the epimerization, which follows the Bilik mechanism, are inversed: the energy barrier is ca. 10 kcal/mol higher in the monodentate geometry than in the bidentate one. Moreover, when the silanol group participates in the reaction, the isomerization reaction is favored over the epimerization by ca. 4 kcal/mol, while when the silanol group is a spectator, the epimerization is favored by ca. 14 kcal/mol. In either the concerted or stepwise mechanism case, analysis of the charge distribution shows that the hydride transfer follows the concerted H + e^- mechanism described above. So, the neighboring silanol group could be essential to the isomerization reaction, while the lack of its involvement results mostly in glucose−mannose epimerization. These calculations now require experimental validation.

2.1.5. Characterization of Lewis Acid Sites of Sn-Beta via Adsorption Studies and Comparison to Other Lewis Acid Catalysts. In order to better understand the nature of the Lewis sites associated with framework Sn, adsorption studies have been carried out with Lewis base probes. Similar to what is found with Brønsted sites formed by framework Al in zeolites,[50] well-defined stoichiometric complexes are also formed by adsorption of a variety of Lewis bases at framework Sn sites.[51] This is most clearly observed with acetonitrile, for which FTIR spectra of acetonitrile-*d*3 at a coverage of one molecule per site exhibit a υ(C−N) stretching frequency at 2312 cm^{-1} that is not observed with nonframework Sn.[52] Stoichiometric adsorption complexes are also observed with simple alcohols,[51] diethyl ether,[51] and ketones, molecules that have the same chemical functionalities as those present in sugars that can be converted by Sn-Beta.

As an example, Figure 5 shows temperature-programmed desorption/thermogravimetric analysis (TPD-TGA) results for acetone following room-temperature adsorption and 1 h evacuation on a Sn-Beta sample that had a Si/Sn ratio of 118 (140 μmol Sn/g).[51] On a purely siliceous Beta, all of the

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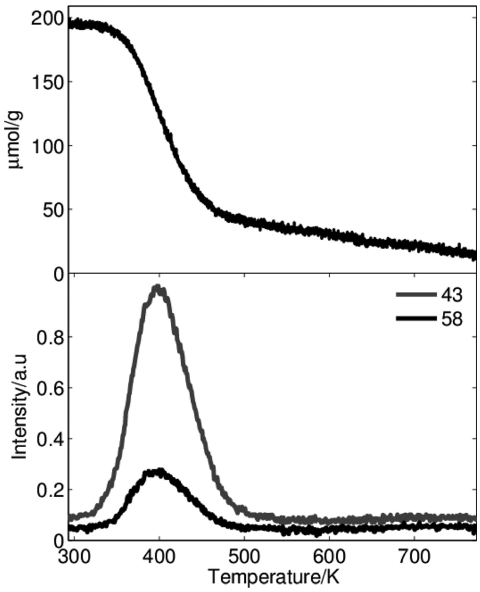


Figure 5. Temperature-programmed desorption (bottom) and thermogravimetric analysis (top) (TPD-TGA) results for acetone following room-temperature adsorption and 1 h evacuation on a Sn-Beta sample.

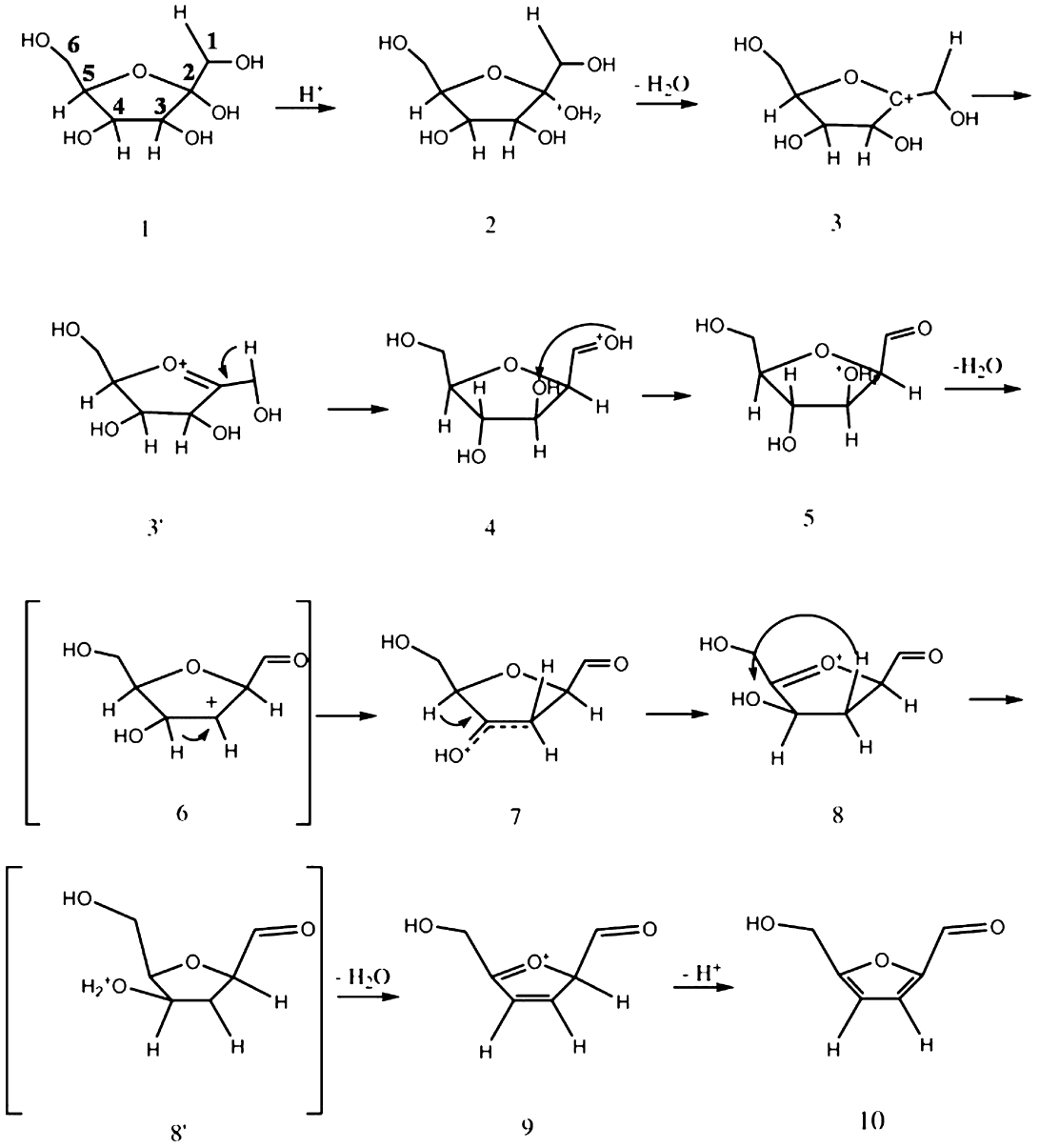
acetone would be removed by room-temperature evacuation; but the initial weight of the Sn-Beta sample indicates that the acetone coverage remains ~200 μmol/g after this pretreatment, implying that acetone remains adsorbed on the Sn sites. The small excess in acetone above the Sn content may be due to the presence of multiple molecules on the Sn sites. During the temperature ramp in TPD, all of the acetone desorbed, with most leaving the sample in a relatively narrow peak centered at 400 K. The relatively high desorption temperature implies that the binding of the carbonyl group to the Sn sites is strong. For comparison purposes, it is worth noting that desorption of acetone from Brønsted acid sites in H-ZSM-5 occurs at 470 K under identical conditions.[53] Calorimetric measurements of acetone in H-ZSM-5 indicated the heat of adsorption is 130 kJ/mol.[53]

It is of interest to compare the Lewis acid sites in Sn-Beta to the Lewis acid sites on other oxides, such as γ-Al_2O_3. In the adsorption of acetone, γ-Al_2O_3 promotes oligomerization of acetone and small aldehydes, possibly due to the close proximity of neighboring sites,[54] so that a comparison of adsorption is not possible. A better comparison comes from observing the dehydration temperature for tert-butanol molecules adsorbed on Sn-Beta and γ-Al_2O_3. On Sn-Beta, dehydration begins at ~370 K in TPD−TGA,[51] whereas for tert-butanol on γ-Al_2O_3, the dehydration reaction is significant only above 400 K.[55] This would suggest that the Sn sites are at least comparable in activity to the sites on γ-Al_2O_3 for some reactions.

Since the polarity of the Sn sites is important for activating molecules for reaction, we also performed calorimetric measurements with CH_3F, a molecule with a large dipole, in Sn-Beta at room temperature. The data shows a well-defined step in the heats of adsorption, from 30 kJ/mol at coverages below 200 μmol/g to 20 kJ/mol at higher coverages. These results are similar to what is observed for polar molecules in Li ion exchanged zeolites,[56] where the heats at high coverages are due to van der Waals interactions of the molecule with the siliceous walls of the zeolite and the higher heats at low coverage are due to the added enthalpic interactions of the molecules with the cations. The results suggest that the additional interaction between CH_3F and the Sn sites is 10 kJ/mol. The fact that the heats of adsorption do not fall until a coverage of 200 μmol/g again suggests that more than one molecule can interact with each Sn site. While insights into the adsorption on the active centers of zeolites have been obtained, the relation between adsorption, activity, and selectivity still remain relatively poorly understood, especially in the liquid phase. Further experimental and computational studies that can lead to rational selection of the active center, the framework in which the active site resides, and the solvent will be highly desirable.

2.2. Sugar Chemistry via Homogeneous Lewis Acid Catalysts. The pioneering work of Zhao et al. showed that metal chlorides dissolved in ionic liquids[57] can catalyze glucose isomerization to fructose followed by dehydration to HMF with yields as high as 70%.[58] DFT calculations and experimental studies (kinetics and X-ray adsorption) in the case of Cr^{2+} and Cr^{3+} systems revealed that isomerization proceeds via the formation of a binuclear complex of glucose with chromium.[59] In particular, while coordination with a single chromium ion could explain the carbohydrate ring opening and closure, calculations showed that a binuclear complex decreased by almost 50% the free energy barrier the H shift (compared to that of the mononuclear complex) required for isomerization.[57] Despite the high yields and important mechanistic findings, reactions in aqueous systems are still preferable and have been conducted by some of the authors. A more recent study of the mechanism of glucose isomerization to fructose using Sn-Beta and homogeneous salts ($CrCl_3$ and $AlCl_3$) revealed striking similarities.[60] Isotopic tracing experiments, starting from glucose labeled with deuterium or ^{13}C in the C2 position, revealed that in all cases isomerization proceeds via an intramolecular hydride transfer from C2 to C1. A kinetic isotope effect (KIE) has also been observed in all cases, when D-labeled glucose at the C2 position was used, indicating that the C2−C1 intramolecular hydride transfer is the rate-limiting step.[60] The production of HMF was also observed when homogeneous salts were used as catalysts, indicating that Brønsted-catalyzed hexose dehydration occurred together with the isomerization. The Brønsted acidity of these mixtures originates from the hydrolysis of the hexa-aquo metal cations ($Cr(H_2O)_6^{3+}$ and $Al(H_2O)_6^{3+}$), which release protons to the solution and form $M(H_2O)_5OH^{2+}$ (M = Cr or Al) species. The glucose isomerization initial rate was found to be proportional to the concentration of these species, calculated using a thermodynamic model of metal speciation in water, indicating that these species are probably the most active ones for isomerization among the different species present in solution.[61] Addition of Brønsted mineral acids to the initial solution decreased isomerization rates by inhibiting the hexa-aquo metal cation hydrolysis, which further corroborates the previous finding about the active species. The similarity of the hexa-aquo hydrolyzed cations with the Sn-Beta open sites further highlights the importance of having a Lewis acid−Brønsted base pair for glucose isomerization in aqueous solutions.[60,61] This finding suggests that studying isomerization in homogeneous-catalyzed systems can provide valuable insights to guide the design of new heterogeneous catalysts with improved performance.

Scheme 3. Schematic of the Fructose Dehydration Mechanism Proposed in Ref 70 (Carbon Atom Numbering Shown in Fructose). Reprinted from Ref 70 Copyright (2011), with permission from Elsevier



2.3. Tandem Reactions. In the case of glucose–fructose isomerization in water, Sn-Beta has been demonstrated to retain reactivity at low pH (e.g., 1) and in the presence of salts (e.g., NaCl). The former allows coupling glucose isomerization with fructose dehydration to HMF, while the latter allows the selective partitioning of products into an organic phase.[62] Given that glucose–fructose isomerization is an equilibrium-limited reaction and that fructose dehydration is an irreversible reaction, the tandem of isomerization and dehydration can drive the reaction to completion. High yields to HMF and furfural (>60%) from glucose and xylose, respectively, can be achieved in a single pot operating as a reactive extractor. As a result, coupling of Lewis acid and Brønsted acid catalysts can potentially lead to both lower capital cost and complete conversion. Moreover, glucose isomerization in ethanol can be coupled with Brønsted acid (Amberlyst 131)-catalyzed dehydration to HMF and subsequent etherification to form 5-ethoxymethylfurfural (EMF) in moderate yield (~30%).[63] Taken together, these examples demonstrate how catalysts, whose properties can be controlled by the materials chemistry at the molecular scale,[64] provide new opportunities for sugar catalysis and biomass processing in liquid media.

3. BRøNSTED ACID-CATALYZED DEHYDRATION CHEMISTRY OF SUGARS

3.1. Homogeneous Brønsted-Catalyzed Dehydration Chemistry. HMF forms by acid-catalyzed hexose dehydration after removal of three water molecules. Fructose dehydration to HMF proceeds much faster and selectively than that of glucose and thus, production of HMF through fructose dehydration is the preferred route. However, despite the numerous studies in the open literature, the fructose dehydration mechanism has not been unambiguously determined. Furthermore, the HMF yields in aqueous mixtures are typically hampered by losses to side products. Dehydration in organic solvents (or in aqueous/organic solvent mixtures), utilization of biphasic reactors, and

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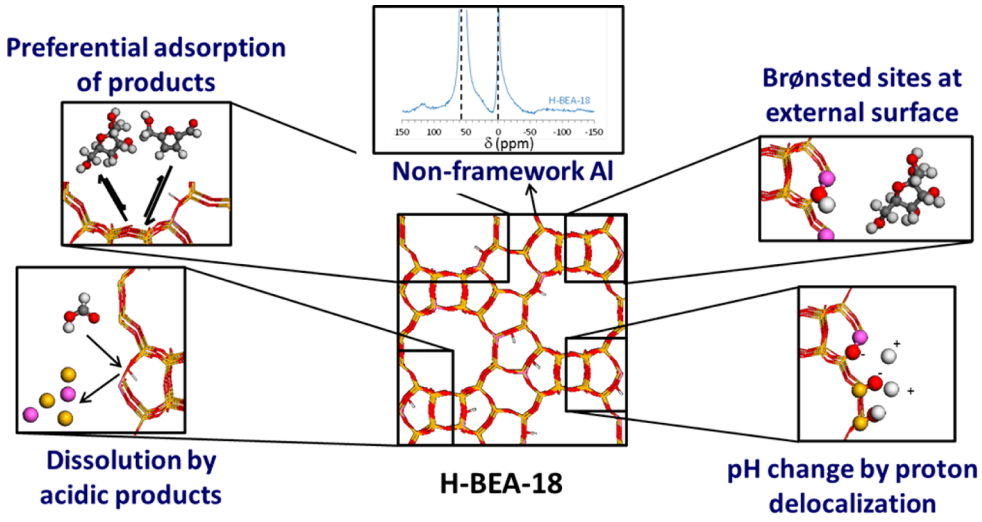

Figure 6. Possible mechanisms by which zeolites could affect fructose dehydration other than Brønsted acid catalysis. Reprinted with permission from ref 75. Copyright 2013 American Chemical Society.

the identification/design of selective catalysts are three approaches commonly used to improve the low HMF yields. Elucidating the mechanisms of Brønsted acid-catalyzed fructose dehydration can provide insights into the design of new catalysts, the rational selection of solvents and cosolvents, and the development of kinetic models for process design.

Previous studies of hexose dehydration in water suggested the formation of cyclic or acyclic intermediates.[6,65−67] In the latter case, dehydration proceeds via the formation of an enediol followed by the removal of three water molecules.[66,67] However, the recent identification of certain intermediates of the cyclic pathway and the absence of deuterium incorporation in HMF, when dehydration is carried out in D_2O, suggest that dehydration does not begin from the open chain fructose tautomer.[68] A gas-phase DFT study of Brønsted acid catalyzed fructose and glucose dehydration screened more than 100 possible reaction schemes, focusing just on the energetics of the stable intermediates (no transition states were isolated).[69] The large number of paths brings out the complexity of the problem. Kinetic and explicit solvent simulations are rare. The mechanism and kinetics of the closed-ring mechanism was studied using quantum mechanics/molecular mechanics simulations that considered explicit water molecules.[70] Even though the protonation of the three hydroxyl groups of the fructofuranose ring was found to be equally probable, the removal of the anomeric carbon hydroxyl was identified as the kinetically most favored pathway. Conversion of fructose to HMF proceeds via multiple elementary steps, some of which are intramolecular hydride and proton transfers (see Scheme 3). The first hydride transfer from C1 to C2 takes place immediately after the first water removal. The second hydride transfer from C4 to C3 occurs immediately after the second water removal and is followed by hydride transfer from C5 to C4 (so that C4 restores its sp^3 hybridization).[70] The high activation energy of these hydride transfers was attributed to polar solvent reorganization.[70]

The high activation energies for the first and third hydride transfer indicate that one of them is probably the rate-limiting step. Experiments using labeled fructose revealed a kinetic isotope effect when fructose labeled at the C1 position was used, indicating that the transfer from C1 to C2 is rate limiting,[71] consistent with the QM/MM-based microkinetic model.[72] By integrating these findings, a skeleton kinetic model was developed that also captures fructose tautomer distribution and a direct path of fructose to formic acid formation to describe quantitatively an extensive set of experimental kinetic data.[71] Fructose dehydration was found to be first-order in proton concentration and in fructose concentration. The model indicates that higher temperatures are favorable because of short contact times and of high selectivities that are retained up to high conversion (at low temperatures, the selectivity drops rapidly with increasing conversion) (i.e., higher temperatures result in a reasonable yield while maintaining high selectivity). Despite this recent progress, identification of intermediates and the effect of organic cosolvents on the mechanism, reaction rates, and selectivities remain poorly understood topics. This lack of knowledge in turn hampers our ability to select cosolvents and build kinetic models that can be used for process optimization.

3.2. Heterogeneous Brønsted-Catalyzed Dehydration Chemistry. Unlike the progress in understanding fructose dehydration in solution, much less is known for this chemistry on heterogeneous catalysts. Catalyst stability and complications arising from the coexistence of Brønsted and Lewis acid sites in real materials, with ratios that can change under reaction conditions, the pore size distribution, the pore hydrophobicity, the adsorption of species from solution, and internal diffusion limitations are some of the key factors that limit our understanding.[73] For example, in the case of propylene glycol dehydration in zeolites, steric hindrance has a profound effect on selectivity compared to catalysts without microporosity.[74]

The possible contributions of aluminosilicate zeolites to the overall chemistry have recently been elucidated (Figure 6).[75] ^1H and ^{13}C NMR experiments indicated that octahedrally coordinated Al atoms, formed during zeolite calcination, act as Lewis acids that catalyze hexose isomerization reactions. Their removal by acid treatment eliminates this pathway, which proceeds in parallel with the dehydration reaction and can account for up to 25% selectivity to glucose.[75] Furthermore, the preferential adsorption of HMF prevents the access of sugars[76] to the acid sites and enhances the rate of undesired reactions starting from HMF over those starting from sugars. As a result, understanding multicomponent adsorption from solution is an essential task that by-and-large has not been addressed (see

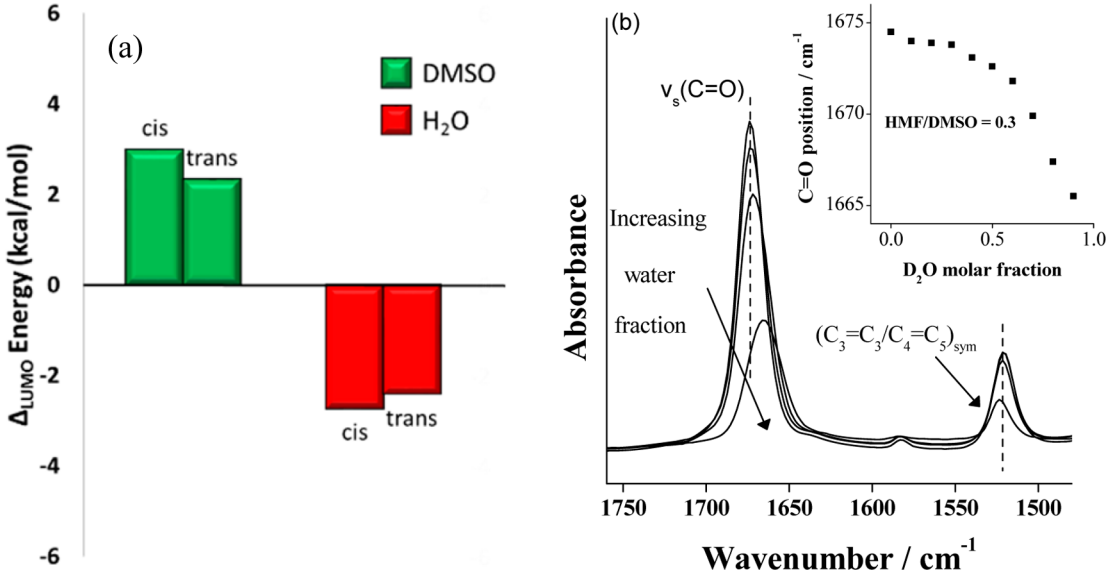

Figure 7. (a) Changes in LUMO energy of isolated HMF cis and trans conformers in implicit DMSO and water as obtained from ab initio calculations. (b) Effect of D_2O on the C═C and C═O stretching vibrations of HMF in HMF/DMSO/D_2O mixtures and constant HMF/DMSO = 0.3 molar ratio. Reprinted in part with permission from ref 89. Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.

below). NMR studies indicate that a small fraction of the zeolite (∼1−2%) dissolves as soluble aluminosilicate species and catalyzes side reactions.[77] While the stability of the zeolite over the typical laboratory experimental timescale does not appear to be an issue, this mechanism needs to be considered in analysis of the experimental data. Reactions on the external surface of the zeolite and homogeneous chemistry, due to pH reduction upon deprotonation of surface silanol groups or Brønsted sites, are additional mechanisms by which zeolites contribute to the overall chemistry. The last two mechanisms, while not as significant under the conditions studied by Kruger et al.,[75] should be considered when analyzing experimental data since the magnitude of contribution is expected to depend on the zeolite loading, the mesoporosity, and the particle size distribution.

Overall, the performance of typical Brønsted acid zeolite catalysts in terms of HMF yield is considerably worse than that of inorganic acids due to the preferential adsorption of the product HMF over sugars in these materials and the subsequent rehydration and polymerization reactions of HMF. It is clear that many more experimental and computational studies are necessary to draw general conclusions about the effects of acid site strength, the microporous environment, the hydrophobicity of the material, cosolvents, etc. and to transform this rather empirical field into fundamental and predictive science.

3.3. Elucidating the Role of Solvents in Activity and Selectivity. Improvements of HMF yield in sugar dehydration have been suggested since the 1950s[78] and follow two general strategies: (1) use of aqueous−organic biphasic reactors, a process known as reactive extraction, and (2) addition of organic cosolvents in water. Specifically, addition of certain cosolvents or NaCl in the aqueous phase can significantly improve the biphasic system performance.[79,80] Several cosolvents screened (e.g., polyethylene glycol,[81] dimethyl sulfoxide (DMSO),[79] poly(1-vinyl-2-pyrrolidinone),[79] acetone[82,83]) reveal that this is a general trend.

In biphasic systems, the hydrophobicity of HMF drives HMF into the organic phase and minimizes side reactions. NaCl results in salting out of HMF, improving HMF yield. A key factor here is to predict the thermodynamics of HMF partitioning in multicomponent systems and identify organic solvents that preferentially solvate HMF, do not mix with water, and allow easy separation of HMF. A general strategy in this direction is still lacking.

In the second strategy of using cosolvents, the underlying physical chemistry is just emerging. We have recently proposed a systematic approach to understanding interactions of biomass derivatives with the solvent and cosolvent, by focusing on the DMSO−water system as a test case and by combining vibrational spectroscopy (Raman, FTIR) with molecular dynamics (MD) simulations.[84] Analysis of ATR/FTIR data indicates that DMSO forms stronger hydrogen bonds with fructose than water (as a hydrogen bond acceptor). In addition, each DMSO molecule interacts with more than one hydroxyl group of fructose and, as a result, its coordination number is less than the number of fructose hydroxyl groups. MD simulations showed that the orientation of DMSO around fructose changes upon addition of small amounts of water, in order to accommodate water molecules in the first coordination shell. In particular, the sulfur atom of the DMSO molecule moves further away from fructose while the oxygen atom of DMSO still interacts with the carbohydrate hydroxyls.[84] Whether these changes in the first co-ordination shell have an effect on fructose dehydration activity or selectivity still remains an open question. Extension of current work to correlate spectroscopic information with reactivity is highly desirable.

Understanding the effect of cosolvent on HMF stability is a difficult problem, primarily because the mechanisms of HMF rehydration to levulinic and formic acids and of HMF polymerization to humins are poorly understood. Nucleophilic attack of water on the C2−C3 carbon atoms of HMF would result in rehydration.[85] On the other hand, it has been proposed that humins can form either via nucleophilic attack of water on the C4−C5 carbons of HMF[85−87] or by nucleophilic attack of the furan ring on the HMF carbonyl.[88] Interrogating these hypotheses experimentally and computationally to derive

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the mechanisms of rehydration and humin formation should be a significant future direction.

To examine the role of solvents in these reactions, we used frontier molecular orbital theory and found that the calculated lowest unoccupied molecular orbitals (LUMO) energy of the HMF molecule in DMSO solvent is higher than in water, which makes it less susceptible to nucleophilic attack in DMSO solvent (Figure 7).[89] To explain the enhanced HMF stability in DMSO−water mixtures, we combined vibrational spectroscopy[89] and molecular dynamics (MD) studies.[90] The ATR/FTIR spectra of the HMF carbonyl (Figure 7b) and hydroxyl regions in HMF−DMSO−water mixtures over a broad range of DMSO−water compositions reveal that DMSO preferentially solvates the HMF carbonyl when the mole fraction of water in the solution is less than ∼0.4, whereas water solvates the HMF hydroxyl.[89] These results confirm from earlier MD simulations.[90] Spectroscopic and molecular simulation studies indicate that the enhanced stability is probably due to selective solvation of the C═O group by the organic solvent. This finding provides a possible means for solvent selection but, as alluded to above, solvation studies, via spectroscopy and simulation, and reaction performance still await a firmer correlation.

4. LIQUID-PHASE ADSORPTIVE SEPARATIONS WITH MICROPOROUS AND MICROMESOPOROUS MATERIALS

The processing of biomass derivatives over porous solid materials (e.g., glucose isomerization in Sn-Beta or dehydration in H-Beta) ultimately involves a series of potentially rate-limiting steps, including micropore-confined diffusion of reactants, products, and even solvents, and their competitive interactions (adsorption/desorption) with active sites therein. While fundamental understanding of the structure−function relations governing such micropore-confined processes has direct implications on tuning reactivity as described previously, it also can be leveraged for exploiting microporous materials, or their hierarchically porous counterparts, for adsorption-based separations and reaction/separation applications. For example, it has recently been demonstrated that a reactive adsorption process using an adsorbent that selectively removes HMF from the aqueous solution can enhance the HMF yield and can be considered as an alternative to reactive extraction.[91]

The CCEI has focused on establishing critical structure−function relations for two primary classes of microporous materials, zeolites and carbons, as adsorbents. The primary aim has been to understand how common factors and forces driving gas-phase adsorption of lower functionality molecules in zeolites and carbons translate to liquid-phase processing of highly functionalized, oxygenated species (e.g., alcohols, polyols, sugars, and furfurals) from aqueous as well as aprotic solvents (e.g., DMSO).[92]

Molecular adsorption onto microporous materials is generally governed by (1) van der Waals interactions with the substrate, (2) electrostatic interactions with charged centers, such as Brønsted acid sites that balance framework Al atoms[93,94] in zeolites or surface oxygenate groups in carbons, and (3) solution thermodynamics, namely, sorbate−sorbate and sorbate−solvent interactions, that govern sorbate and solvent partitioning between phases. Fundamental insights into structure−function relations governing how these factors contribute specifically to adsorption of oxygenated species has been a focus of the CCEI, achieved through synergistic experiments and new molecular simulation schemes;[95−97] the latter have been specifically tailored to accurately capture thermodynamics of adsorption from the liquid phase. Insights into the roles of hydrophobicity and intrinsic or designed function of the pore environment in selective adsorption, and highly selective reactions facilitated by these microporous systems in turn, have been a key driver of research.

4.1. Adsorption of Oxygenated Species from Aqueous Solutions onto Hydrophobic Materials. As has been well-established for linear and branched alkanes,[98−103] the strong adsorbate confinement imposed by zeolitic pores results in large influence of van der Waals forces on molecular adsorption as manifested through dramatic and systematic increase in the heats of adsorption, equilibrium constants for adsorption (K_{ads}), and Henry's constants with increasing carbon number and reduction in pore size. In an effort to bridge from gas to liquid phase processing, comparative studies of vapor and liquid-phase adsorption of oxygenated species (e.g., alcohols, polyols) have been carried out over small (e.g., FER), medium (e.g., MWW, MFI/H-ZSM-5, BEA), and large-pore (e.g., MOR, FAU) or hierarchically porous zeolites (e.g., SPP[104,105]). These studies reveal that oxygenate adsorption, like adsorption of linear and branched alkanes, remains strongly influenced by dispersion forces.[106] Specifically, for adsorption at low loadings, increase in the carbon number of alcohols and polyols with comparable −OH functionality (i.e., number and geometry) results in enhanced adsorption and systematic increases in Henry's constant. Measured exponential increase of K_{ads} with an increasing carbon number implies a concomitant linear increase in the free energy of adsorption, owing to intensifying dispersion interactions with increasing size of the oxygenated compound.[106]

At higher loadings, liquid- and gas-phase adsorption of alcohols and polyols exhibits a decrease in the extent of adsorption with increasing carbon number because of the finite pore volume and the concomitant difficulty in accommodating bulkier molecules.[97] Specifically, adsorption of short- over long-chain alcohols and linear over branched alcohols and polyols of equal −OH number was consistently measured.[107,108] Molecular simulations predict the same behavior,[97] with deviations from experiments attributed to framework flexibility[95] and intrinsic silanol defects[109] within zeolites that are not often accounted for in first-principles calculations.

While gas- and liquid-phase adsorption of alcohols and polyols over zeolites share characteristic dispersion effects, significant distinctions between phases derive from specific implications of oxygenate functionality.[106] Namely, whereas changes in the −OH number of polyols are positively correlated with changes in Henry's constant for gas-phase adsorption on zeolites, Henry's constants are found to decrease with increasing −OH number in liquid-phase adsorption.[97,106] Ultimately, unraveling the origins of such differences in behavior of oxygenate functionality in liquid-phase adsorption is of critical importance for understanding and rationally controlling biomass processing over microporous solids. In the case of zeolites, it requires fundamental insight into OH-mediated interactions with intrinsic silanol defects and modulated Brønsted acidity (i.e., Si/Al ratio), as well as the impact of oxygenate functionality on solution phase thermodynamics and thus partitioning of both adsorbate and solvent between bulk and micropore-confined phases.

In the case of aqueous solvents, both experiments and simulations have shown that a small but finite amount of water

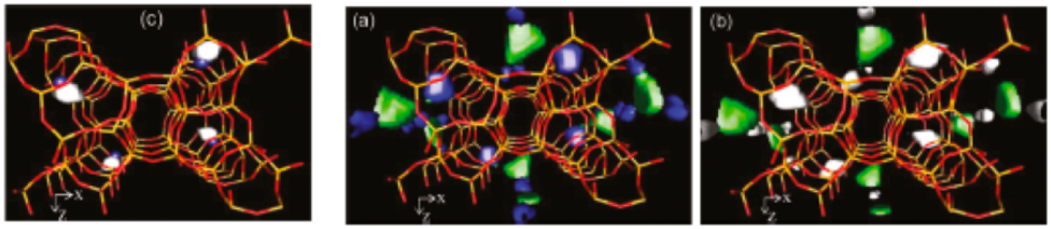

Figure 8. Isodensity surfaces for ethanol/water and methanol/water adsorption in silicalite-1 wherein (left) water-free ethanol/methanol adsorption occurs in sinusoidal channels at high densities (~800 mol/m^3) and expands to straight channels as facilitated by water adsorption as shown separately for (center) methanol and (right) ethanol (green isodensity profiles in center, right correspond to water adsorption). Reprinted in part and adapted with permission from ref 96. Copyright 2011 American Chemical Society.

adsorbs even within hydrophobic zeolite pores.[96] Explicit water adsorption, however, is often neglected from analysis by molecular simulation of aqueous phase adsorption due to complexity of its inclusion and on the justification of its relatively weak binding in hydrophobic pores and even on Brønsted sites therein.[94,110] Yet, recent molecular simulations (Figure 8) have revealed that quantification of water adsorption within zeolitic pores is critical for interpreting and predicting alcohol and polyol adsorption from aqueous mixtures. Namely, water clusters have been observed to form within hydrophobic zeolite channels at sites (e.g., straight channels in MFI zeolite) that are distinct from those common to adsorbed oxygenates (e.g., sinusoidal channels and intersections in MFI zeolite). Anisotropic framework flexibility[95] can facilitate such water adsorption. Namely, as shown for furfural adsorption from aqueous solutions onto silicalite, oxygenate adsorption results in pore expansion that pushes water into and contracts typically unoccupied regions of the zeolite framework. The adsorption of water within zeolite structures introduces effective hydrogen-bonding adsorption sites in zeolitic micropores that serve to enhance the extent of adsorption of oxygenated species relative to pure-component adsorption levels.[96,109]

The extent of water adsorption is ultimately sensitive to polarity of the zeolite pores, a property that can be tuned by (1) structural silanol defects[109,111,112] formed during zeolite synthesis and (2) Brønsted acidity[94,110] introduced by varying the Si/Al ratio. Recent studies[109] have compared vapor (i.e., water-free) and aqueous phase adsorption of polyols [e.g., ethylene glycol (EG) and propylene glycol (PG)] in zeolites whose density of silanols was tuned via synthetic methods (e.g., fluoride-mediated nondefected structures[113] and defected alkaline-mediated and steamed structures[114]). Water-free oxygenate adsorption reveals an enhancement of adsorption propensity with increasing silanol defect density. This underscores the importance of possible hydrogen bonding between oxygenate functionality and silanols. Water is found to hinder oxygenate adsorption at low concentrations, owing possibly to the effect of competitive adsorption in the presence of excess water despite the relatively low heat of adsorption of water. At higher loadings, however, the extent of oxygenate adsorption exceeds water-free levels and grows with increasing silanol defect density (Figure 9). This suggests that both direct interactions between adsorbates and defect sites as well as water-mediated interaction with those sites play a key role in dramatically tuning the extent of adsorption.

More commonly recognized control over micropore polarity derives from incorporation of Brønsted acid sites,[93,94] with the corresponding hydrophobicity/hydrophilicity of the pores modulated by respective increase/decrease in the Si/Al ratio. While experiments show that enthalpies of adsorption increase

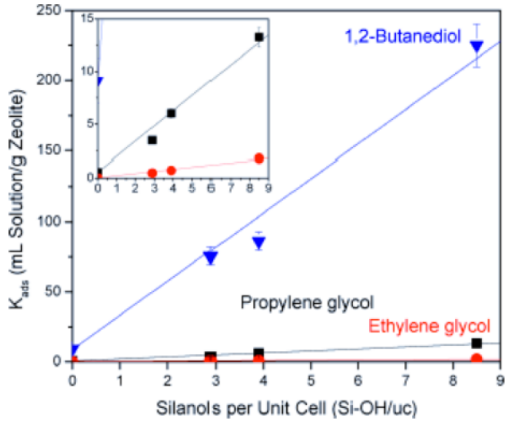

Figure 9. Linear correlation of K_{ads} with silanol density of silicalite-1 zeolite for three surrogate oxygenated molecules. Reprinted with permission from ref 109. Copyright 2013 American Chemical Society.

with decreasing Si/Al ratio, a compensating increase in adsorption entropy results in limited overall sensitivity of the apparent total free energy of adsorption and, thereby, the measured extent of adsorption, to Si/Al ratio.[102] This apparent modest sensitivity to the Si/Al ratio, including a small but measurable reduction in K_{ads} with decreasing Si/Al ratio, has been attributed to effects spanning competitive water adsorption[115] to partial blockage of preferred adsorption sites by Brønsted acid site protons.[106] This apparent lack of sensitivity is surprising given the large impact of the silanol defect density on adsorption described above. In fact, it is conceivable, and has been proposed, that a significant sensitivity to the Si/Al ratio may actually exist but may simply be masked by adsorption on silanol defects intrinsic to zeolitic materials.[109]

Beyond impact of the functional features of the adsorbent itself, the nature of the oxygenated adsorbate, namely the specific identity and number of oxygenate groups, has been identified as a highly impactful factor governing liquid phase adsorption of polyfunctional molecules.[97,106] The reduction in adsorption affinity associated with the addition of one −OH group to an alcohol or polyol has been shown, in the case of the zeolite MFI, to be nearly equally offset by the increase in adsorption affinity associated with an increase in carbon number (i.e., dispersion forces).[106] The identity of the hydroxyl group also appears critical. Whereas conversion of −OH to =O on primary carbons reduces adsorption by 10−90%, the same change in oxygenate functionality on a secondary carbon results in a 200−400% increase in adsorption.[116] These trends with oxygenate functionality can be explained at least qualitatively based upon corresponding changes in polarity of the adsorbates. Specifically, a positive linear correlation exists

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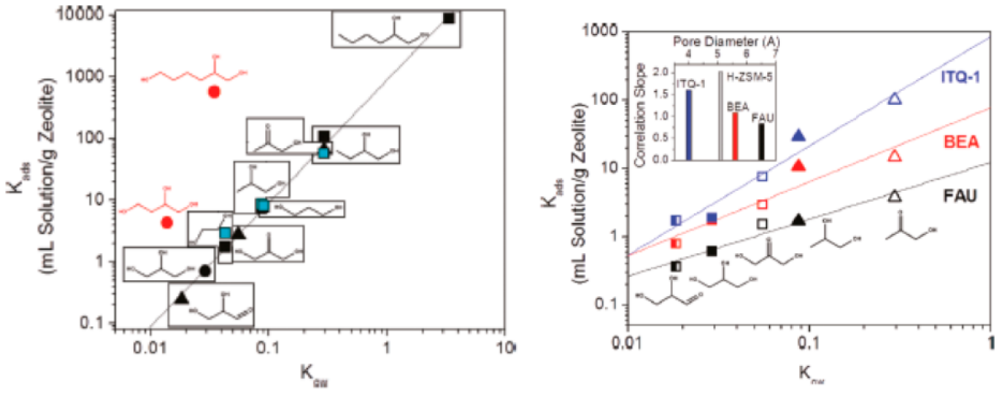

Figure 10. Correlation of K_{ads} with octanol–water partition coefficient, K_{OW} for adsorption of various specified oxygenated molecules over MFI zeolite (left) and FAU, BEA, and ITQ-1 zeolites (right). Adapted with permission from ref 116. Copyright 2011 American Chemical Society.

between measured K_{ads} and the octanol–water partition coefficient (K_{OW}), the latter of which can be calculated by established methods for a given molecule (Figure 10).[116] This simply underscores the influence of the hydrophobic nature of the zeolite micropore. The correlation, developed and tested for polyfunctional oxygenates on H-ZSM-5, appears applicable for predicting relative adsorption affinity in medium and large-pore zeolites.

K_{OW} does not, however, exclusively describe the functionality of K_{ads} for oxygenated species given the complex dependency of the latter upon adsorbent-specific factors, such as dispersion forces and hydrogen bonding, among others. This complexity is underscored by the linkage of measured ($K_{ads,meas}$) and intrinsic ($K_{ads,int}$) values for K_{ads} by the infinite dilution activity coefficient, γ, namely, $K_{ads,meas} = \gamma K_{ads,int}$. In this context, it has been shown that increasing the carbon number, for example in the case of diols, leads to a decrease in water solubility and an increase in dispersion forces. Moreover, an increase in the −OH number for alcohol–diol pairs (e.g., 1-propanol and 1,2-propanediol and 1-butanol and 1,2-butanediol) is accompanied by an order of magnitude reduction in corresponding activity coefficients. This indicates the apparent implications of solution phase thermodynamics, captured by the activity coefficient, for understanding the inverse proportionality of K_{ads} and −OH number.

While the qualitative correlations and structure–function relations described above generally hold for oxygenate adsorption on medium and large-pore zeolites, they tend to break down for small-pore zeolites (e.g., FER).[106] Even qualitative reversal of trends on smaller pore zeolites is a result, at least in part, of issues with complete inaccessibility or only partial accessibility of polyfunctional molecules in the zeolite pores, a finding that is consistent with trends for linear and branched alkanes.[117,118] This is reflected best by the K_{ads}–K_{OW} correlation described above, wherein adsorption behavior for various oxygenated molecules on a specific zeolite appears universally and linearly correlated with K_{OW}, differentiated only by the specific adsorbent.[116] In the case of small-pore zeolites, linear K_{ads}–K_{OW} relations related to specific adsorbents are further differentiated by commonalities in adsorbate configuration (e.g., partial insertion in zeolite pores, weak interactions with external surfaces) on the adsorbent.

Solvent coadsorption could also have an effect on the determination of the adsorbed loading. The adsorption loading is typically considered to be equal to the change in solute concentration multiplied by the initial volume of the solution, which assumes that the volume changes of the solution due to adsorption are negligible. However, this assumption might not hold when there is significant coadsorption of the solvent or in the case of significant changes of the liquid phase density due to composition. The loadings measured using this approach are called "excess adsorption" and can be considered as a good approximation of the real loadings only when the coadsorption of the solvent is not significant. Several different approaches have been considered in the literature for estimating real adsorption from the excess adsorption data.[119−125] Each one is based on different assumptions about the adsorbed phase and the adsorbent and are probably not valid for sugar chemistry.[76] To alleviate this issue, a model has been proposed that considers that the entire zeolite pore volume, determined from N_2 physisorption, is filled either with solvent or with solute.[76] Using this approach, it was found that the excess adsorption loadings of HMF and levulinic acid from aqueous solutions in high Al content zeolite Beta are good approximation of the real ones, but differences of 30% to 50% are expected for the adsorption of formic acid and sugars.[76] Direct real adsorption measurements and development of predictive adsorption models are needed for understanding separation and kinetics in microporous materials.

4.2. Structure–Function Relations for Sorbents in Aprotic Solvents. In addition to biomass processing in pure aqueous solvents, aprotic solvents (e.g., DMSO) have shown promising reaction selectivity for fructose derivatives like HMF.[65,79,126−129] The resulting system, however, faces subsequent challenges with the purification of HMF from DMSO,[65,130] owing to the high boiling temperature of DMSO, which precludes application of conventional distillation strategies and demands alternatives, such as adsorption, for selective separation. While HMF adsorption from aqueous solutions has been demonstrated to occur in hydrophobic zeolites [e.g., silicalite-1, dealuminated Y (DAY)] with rapid pore saturation at low concentrations (0.2% HMF), achieving similar adsorption from mixed DMSO/water or pure DMSO solutions has proven challenging. In the limit of pure aqueous (i.e., DMSO-free) solutions, larger-pore DAY zeolites accommodate significant water adsorption in addition to HMF, with selectivity for HMF over water adsorption improved by a factor of 3 for the more confining and less defective (i.e., lower silanol group content) pores of silicalite-1.

Upon increasing the amount of the aprotic cosolvent, DMSO, a condition required for improving reaction selectivity, dramatic reduction in HMF adsorption to near negligible levels

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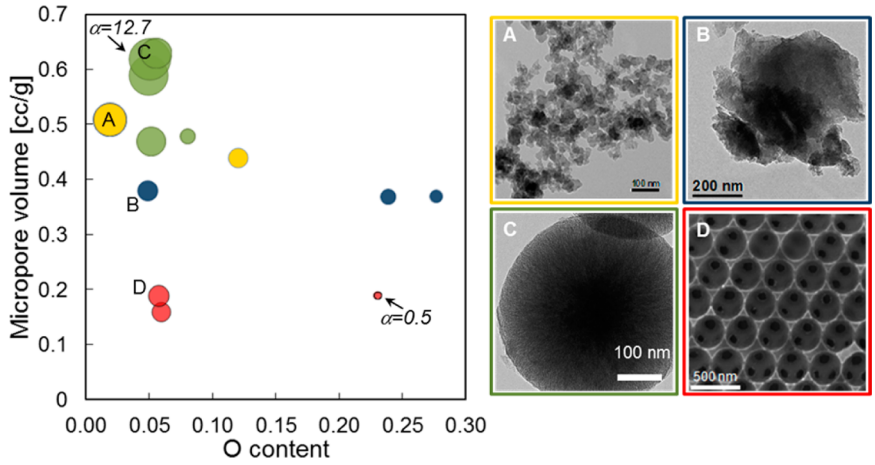

Figure 11. Parametric dependence (left) of HMF adsorption selectivity (α, proportional to symbol size over the specified range) on sample micropore volume and polarity as measured by elemental oxygen content for four classes of carbons, including two commercial carbons (A: BP2000 and B: Norit1240) and two synthetic carbons (C: micromesoporous carbon and D: macroporous carbon). Adapted from ref 133. Copyright (2014), with permission from Elsevier.

is observed over both silicalite-1 and DAY zeolites.[131] This is attributed to partitioning of HMF, a molecule with hydrophobic character, into DMSO instead of into water as a result of more hydrogen bonding between HMF and DMSO than between HMF and water (see Elucidating the Role of Solvents in Activity and Selectivity). Therefore, as DMSO content is increased, the driving force for HMF adsorption weakens, with HMF thermodynamically preferring to remain solvated by DMSO. Given the dominant entropic contribution to free energy of adsorption for multicomponent systems, the poor affinity of HMF for adsorption from DMSO-containing solutions onto hydrophobic zeolites underscores the need for materials for which enthalpic interactions of HMF are significantly higher than those for DMSO and water.

To this end, screening of commercially available activated carbons for their propensity to selectively adsorb HMF from DMSO-containing solutions has identified several (e.g., BP2000 and Norit1240) that display significant HMF adsorption even from pure DMSO solutions, albeit at levels that are still less than those achievable from pure water.[132] Addition of cosorbent fructose is found to enhance the capacity for HMF adsorption without significant adsorption of fructose itself. Thus, activated carbons in general appear as promising candidates for selective HMF adsorption from DMSO solutions containing unreacted fructose. Recent comparative quantitative analysis[133] of carbon texture, elemental composition, surface functionality, and HMF/fructose adsorption capacities of two promising commercial carbons (BP2000, Norit1240) and one synthetic macroporous carbon[134,135] revealed two key handles for tuning HMF adsorption selectivity: carbon polarity and ultramicropore volume, namely, the pore volume associated with pores less than 1 nm in diameter (Figure 11). Specifically, with micropore volume held constant, reduction of the elemental oxygen content, distributed among oxygenate species including prominent carboxylate, and minor lactone, carboxylic, and phenolic groups, leads to an increase in HMF adsorption capacity and reduction of fructose capacity. The concomitant increase in HMF adsorption selectivity upon increasing the hydrophobicity of the carbons appears to exploit differences in the hydrophobic and hydrophilic character of HMF and fructose, respectively.

Likewise, with oxygen content and its distribution among various oxygenate species held constant, HMF adsorption selectivity has been linked to modulation of specific textural properties of the carbon sorbents. While sensitive to properties like total surface area and total pore volume, HMF adsorption selectivity appears most sensitive, especially at higher concentrations of adsorbates, to an ultramicropore volume of carbon sorbents. This ultramicropore volume is ultimately a textural measure of the features of the carbon sorbent related to strongest confinement of the adsorbate molecule, and thus provides insight into the possible important role of dispersion forces in adsorption of hydrophobic molecules within nonpolar carbon micropores.

The resulting design rules and fundamental insight into structure–function relations governing adsorption of oxygenated species in microporous carbons have subsequently been validated and exploited in order to derive a class of synthetic micromesoporous carbon sorbents with attractive properties spanning microstructure, surface chemistry, and morphology. Specifically, sacrificial hard templating on submicron Al-incorporated mesoporous silica particles yields spherical mesoporous carbon particles, the size and shape of which are attractive for ease of processing relative to finer commercial carbons (e.g., BP2000) that tend to form slurries that confound sorbent/solvent separation. The synthetic materials offer a mesoporous carbon structure that is capable of withstanding systematic high-temperature reduction and CO_2 activation employed, respectively, to minimize oxygenate functionality/polarity and to maximize the ultramicropore volume while raising the specific surface area to ca. 1500 m^2 g^{-1}. This combination of large ultramicropore volume and low polarity in a coarse, high surface area synthetic carbon helps realize HMF adsorption selectivities in an easily processed carbon that exceeds those of the best performing commercial carbons by more than 60%.

5. SUMMARY AND OUTLOOK

In the introduction of this paper, we outlined overarching challenges in converting sugars to intermediate platforms and then summarized the progress made by CCEI researchers to overcome these challenges. One of our earlier discoveries was the use of solid Lewis acid catalysts, such as Sn-Beta and Ti-

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Beta, to selectively catalyze glucose to fructose isomerization in liquid water. This demarcates the first heterogeneous catalyst for this transformation, offering an advantageous alternative to immobilized enzyme-catalyzed isomerization processes practiced currently and which require strict regulation of temperature, pH, and impurity content. Moreover, glucose can be epimerized to mannose via a Bilik-type mechanism of C3 carbon shift from the C2 to C1 position in methanol solvent and in borate salts in water. In addition, we showed the first direct and stereospecific isomerization of D-glucose to L-sorbose using Ti-Beta zeolite, a reaction without any precedent in the enzyme or homogeneous catalysis literature and the extension of C2−C1 hydride shift isomerization chemistry to C5 sugars and glucose-containing disaccharides.

Interestingly, the exact location of the active catalytic centers, the hydrophobicity of the solid materials that isolate them, and the properties of the solvent are all key factors in controlling the chemistry at the molecular level. A combination of kinetics, isotopic tracing, spectroscopic studies, and simulations exposed the possibility of a rather intriguing cooperativity, as often encountered in enzymatic catalysis, of the Lewis acid center, the stannanol site, and the proximal silanol group in determining whether glucose isomerization to fructose or epimerization to mannose occurs. The mechanistic similarity of homogeneous Lewis acid salt-based catalysts (e.g., $CrCl_3$ and $AlCl_3$) to our earlier heterogeneous Sn-Beta zeolite has been remarkable and provides a means to guide selection and design of heterogeneous catalysts by understanding the chemical principles of homogeneous Lewis acid catalysts.

The stability of this class of heterogeneous Lewis acid catalysts even at low pH opens up new horizons in coupling Lewis and Brønsted acid-catalyzed chemistry. Brønsted acids catalyze hydrolysis, dehydration, and etherification reactions and enabled us to couple aldose (glucose and xylose) isomerization to ketose (fructose and xylulose) and subsequent dehydration to furan (HMF and furfural) in a single pot. This tandem of isomerization and dehydration reactions overcomes the equilibrium limitations of the isomerization reaction, and when carried in a biphasic system results in significant yields to HMF from glucose and furfural from xylose for the first time. HMF and furfural can then be used as intermediate platform molecules to create a wide range of intermediates useful in the production of biofuels and biochemicals. Therefore, the development of catalytic systems that can couple glucose transformation into HMF and its extension to smaller sugars (e.g., xylose transformation to furfural) represents a technical breakthrough on the road to developing processes for biomass transformation into biofuels and biochemicals. Despite remarkable progress on mechanistic understanding, solvent−solute−catalyst interactions still remain not as well understood, and in situ characterization of the active site and operando spectroscopy that directly reveals the site cooperativity manifested computationally in sugar transformations are important topics for future work.

Sn-beta zeolites are typically synthesized in fluoride media and require long crystallization times, highlighting the need for developing more efficient synthesis methods. The use of seeded growth using dealuminated beta nanocrystals,[136] dealumination followed by solid state ion exchange,[137] or steam-assisted crystallization of Sn containing dry gels[138] are a few of the alternative methods explored for reducing the Sn-beta crystallization time. However, this is an area with more room to explore. Furthermore, the development of synthesis protocols for the crystallization of Sn-beta with hierarchical micro- and mesoporosity could have a profound impact since such materials could provide the means for controlling selectivity to parallel reactions, control deactivation, and gain better understanding about the interaction of solvent and solute with the active sites.

While the Brønsted acid catalyzed fructose dehydration in inorganic solvents has been studied intensively over the years, its mechanism has been rather poorly understood. The combination of kinetics and isotopic labeling experiments, guided from first-principles multiscale simulations, has provided for the first time insights into the mechanism, such as the first hydride transfer upon water removal being the rate-limiting step. Quantum mechanics/molecular mechanics (QM/MM) molecular dynamics (MD) simulations showed that rate-limiting hydride or proton transfer elementary steps are profoundly influenced by solvent dynamics and reorganization, being accelerated as the dielectric constant of the medium decreases. Analysis of spectroscopic data with the help of ab initio and molecular simulation has revealed that preferential solvation of the carbonyl group of HMF by organic cosolvents, such as DMSO, is potentially responsible for the enhanced stability of HMF and the improved selectivity in mixed solvents. Aside from a shielding effect provided by the cosolvent, the concomitant increase in the energy of the lowest unoccupied molecular orbital (LUMO) makes HMF less susceptible to nucleophilic attack (i.e., rehydration and polymerization). This insight provides a handle on selecting solvents and improving performance. Yet, a direct connection between solvation effects and reactivity studies is still lacking and is an excellent topic for future research that may eventually enable rational selection of solvents and catalysts.

We have also shown that it is entirely possible to reveal the mechanisms of Brønsted acid zeolite catalysts using a multitude of techniques to follow the speciation and chemistry in solution and the adsorption of multicomponent systems and by controlling the active centers during synthesis or by post-treatment of zeolites. Differences in the preparation method and/or even in the amount of zeolite can lead to different contributions from various mechanisms at work, rationalizing the lack of consensus among published experimental studies. Following a simple experimental protocol we proposed is critical in order to provide reproducible and interpretable data. Developing quantitative models that can account for adsorption and diffusion in microporous materials along with the effects of pore size and solvent on activity and selectivity is essential.

In order to improve HMF and furfural yield, we introduced new micro- and micromesoporous carbon adsorbents that can selectively remove HMF from fructose−water or water−DMSO mixtures, enabling highly selective reaction−adsorption systems with improved selectivity to HMF or other products like levulinic acid. In parallel, in order to provide insights into the reaction in microporous materials, such as zeolites, we have conducted fundamental adsorption studies. We have shown via molecular simulation how the preferential solvation of various biomass species brings out yet another role of solvents in controlling partitioning of species between the two phases (solution and solid). Adsorption even of the single component from solution is complicated by the difficult-to-quantify coadsorption of the solvent. Development of techniques that can directly measure adsorption of all species, including the solvent, from liquid mixtures will bring significant advances to this field.

Despite the aforementioned advances in understanding solvation, mechanisms, and cooperativity of active centers in Lewis and Brønsted acid-catalyzed sugar chemistry, we still lack quantitative descriptors that would allow us to rationally select suitable solvents and heterogeneous catalysts. Many effects of changing the solvent in this chemistry still remain unknown, such as to what extent it would change the rate-limiting steps in identified and known mechanisms or even the reaction path or mechanism altogether, which greatly increases the complexity of the problem. There are also additional reaction steps, catalysts, and solvents that will need to be coupled to integrate upstream from sugars to (hemi)cellulosic biomass, and downstream from furanic compounds to useful biofuels or biochemicals. As a result, the transformation of interpretive science we experience currently into the desired predictive science and ultimately into processes for the practical conversion of biomass as a renewable energy source will require further scientific and technological developments.

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Notes

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